A long duration of the prediagnostic symptomatic interval is not associated with an unfavourable prognosis in childhood medulloblastoma

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Abstract: BACKGROUND: Due to the lacking specificity of symptoms making a correct diagnosis can be a challenge in children with medulloblastoma. This can lead to prediagnostic symptomatic intervals (PSIs) of several weeks to months. It is unknown whether the length of the PSI is associated with an inferior survival outcome in this population. METHODS: To study the association of PSI with disease stage at diagnosis, tumour control and survival in children with medulloblastoma, prospectively collected data on PSI, clinical, and biological features were analysed in 224 patients diagnosed at the age of 3-18years and treated within the prospective randomised multicentre trial HIT'91. RESULTS: Patients with lower-stage disease tended towards a longer median PSI than those with higher-stage disease (M0 stage, 2.0months; M1 stage, 2.0months; M2/M3 stage, 1month; p=0.094. M0/1 stage versus M2/3 stage; p=0.025). The patient group with the longest PSI had the best survival outcome (PSI 4.0months: 10-year overall survival rate (OS), 71%; PSI <4.0months, 10-year OS, 61%; p=0.056). Age at diagnosis was positively correlated with PSI (p=0.027). No associations were found between PSI and sex histological subtype, presence of postoperative residual tumour, or c-myc and TrkC mRNA expression. CONCLUSION: Contrary to a common belief that a longer PSI may adversely affect prognosis, a longer PSI was associated with a trend towards lower metastatic stage and better survival probabilities. Nevertheless these findings do not obviate the importance of a timely diagnosis in paediatric patients with medulloblastoma.

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A long duration of the prediagnostic symptomatic interval is not associated with an unfavorable prognosis in childhood medulloblastoma

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ABSTRACT

BACKGROUND: Due to the lacking specificity of symptoms making a correct diagnosis can be a challenge in children with medulloblastoma. This can lead to prediagnostic symptomatic intervals (PSIs) of several weeks to months. It is unknown whether the length of the PSI is associated with an inferior survival outcome in this population.

METHODS: To study the association of PSI with disease stage at diagnosis as well as tumor control and survival in children with medulloblastoma, prospectively collected data on PSI, clinical, and biological features were analyzed in 224 patients diagnosed at the age of 3 - 18 years and treated within the prospective randomized multicenter trial HIT'91.

RESULTS: Patients with lower-stage disease tended towards a longer median PSI than those with higher-stage disease (M0 stage, 2.0 months; M1 stage, 2.0 months; M2/M3 stage, 1 month; p=0.094. M0/1 stage vs. M2/3 stage; p=0.025). The patient group with the longest PSI had the best survival outcome (PSI ≥4.0 months: 10-year overall survival rate (OS), 71%; PSI <4.0 months, 10-year OS, 61%; p=0.056). Age at diagnosis was positively correlated with PSI (p=0.027). No associations were found between PSI and gender, histological subtype, presence of postoperative residual tumor, or c-myc and TrkC mRNA expression.

CONCLUSION: Contrary to a common belief that a longer PSI may adversely affect prognosis, a longer PSI was associated with a trend towards lower metastatic stage and better survival probabilities. Nevertheless these findings do not obviate the importance of a timely diagnosis in pediatric patients with medulloblastoma.

1. INTRODUCTION

Medulloblastoma is a primitive neuroectodermal tumor of the cerebellum with a tendency to metastasize by leptomeningeal spread. It is the most common malignant brain tumor in pediatric patients accounting for 20% of all central nervous system tumors. Advances in diagnostic, surgical, radiotherapeutic and chemotherapeutic methods have led to markedly improved survival outcome in the last decades. However, a significant proportion of patients still succumb to their disease.[1-2]

Making a correct diagnosis can be a challenge due to often non-specific symptoms and signs which not only depend on the tumor itself, but also on the patient's age and developmental stage.[3] This can lead to prediagnostic symptomatic intervals (PSI) ('diagnostic time lags') in the range of several weeks to months.[4-11] The assumption that a longer PSI may result in a more advanced disease stage and/or have an adverse impact on tumor control, survival and/or neurological/neuropsychological/quality of survival outcome may lead to self-reproaches from parents and physicians and can result in accusations of medical malpractice.[12-14] However, available information on the correctness of this assumption is insufficient, as studies on PSI in children with brain tumors suffer from low patient numbers, retrospective design, heterogeneity of patient, disease, and treatment characteristics, and lacking outcome data.[4-11, 15-24]

To study the association of the PSI with disease stage at diagnosis as well as tumor control and survival outcome, we analyzed prospectively collected data on 224 homogeneously treated patients.

2. METHODS

2.1. Patients and diagnostic procedures

Between August 1991 and December 1997, 280 patients 3 -18 years of age with newly diagnosed medulloblastoma were treated according to the prospective randomized multicenter HIT‘91 trial, as previously described.[2, 25] Recommended staging included pre- and postoperative cranial magnetic resonance imaging (MRI) or computed tomography (CT), spinal MRI, and evaluation of cerebrospinal fluid (CSF) cytology.[26] Central review of histopathology, CSF cytology, and CT/MRI scans was recommended. mRNA expression levels of c-myc and TrkC in tumor tissue were measured as described.[27] Duration of the prediagnostic symptomatic interval (PSI), i.e. the interval between the appearance of the first symptom/sign judged as unambiguously related to the tumor disease by the treating oncologist, as well as the nature of the presenting symptoms and signs were prospectively recorded. A PSI value was available for 266 of 280 (95%) patients. The current analysis is restricted to those 224 of 280 (80%) patients for whom the PSI value and central histopathological review of tumor tissue were available. Complete radiology/cerebrospinal fluid staging for metastases was performed in 184 (82%) of the 224 study patients.

2.2. Treatment

After obtaining approval of the study protocol from the appropriate ethical committees and informed consent from all patients and/or their legal representatives, patients were randomly assigned to receive either immediate post-operative radiotherapy

(35.2 Gray [Gy] to the craniospinal axis followed by a boost to the posterior fossa to a total of 55.2 Gy and to any supratentorial and spinal metastases to 50.0 Gy, with concomitant vincristine) followed by 'maintenance' chemotherapy (CCNU, vincristine, and cisplatin); or immediate post-operative pre-radiation 'sandwich' chemotherapy (ifosfamide, etoposide, methotrexate, cisplatin, and cytarabine) followed by radiotherapy and, in case of non-complete response thereafter, additional 'maintenance' chemotherapy, as previously described.[2, 25]

2.3. Statistical analyses

Kaplan–Meier estimates and log-rank test were used for overall survival (OS) and progression-free survival (PFS) rates (±standard errors), with OS measured from primary surgery to death of any cause or last evaluation, whichever came first, and PFS measured from primary surgery to first documented progressive disease, to death of any cause, or to last evaluation, whichever came first. To analyze the association of the duration of the PSI with survival, patients were divided into quartiles according to their PSI. For multivariable analyses, Cox regression models with forward and backward stepwise selection (inclusion criterion: p-value of the score test ≤0.05, exclusion criterion: p-value of the likelihood ratio test ≥0.10) were used to analyze the possible impact of the following variables: age (continuous and categorical [3-8 vs. 8-13 vs. 13-18]), sex (categorical), stage (categorical: M0 vs. M1 vs. M2/3 vs. incomplete staging; M0/1 vs. M2/3 vs. incomplete staging; M0 vs. M1/2/3 vs. incomplete staging), histological subtype (categorical, classic vs. desmoplastic vs. large cell/anaplastic), residual tumor (categorical), therapy arm (categorical), PSI (continuous and categorical [group]), c-myc mRNA expression (categorical [≤1 vs. >1 vs. no value available]), and TrkC mRNA expression (categorical [≤1 vs. >1 vs. no

value available]). For Cox regression, p-values of likelihood ratio test were calculated. In order to assess potential associations between the patient characteristics and PSI, the log-rank test was used. To compare the frequency of symptoms between different patient groups divided according to categorical age or metastatic stage, Fisher's exact test was used. All p-values were considered as explorative, no significance level was fixed. Analyses were performed with SPSS software, version 16.0.

3. RESULTS

3.1. Patient and disease characteristics and presenting symptoms

Patient and disease characteristics of the 224 study patients are summarized in Table 1. The most frequent presenting symptoms were headache, vomiting, ataxia, diplopia/squint, and vertigo/dizziness (Table 2). Headache and vertigo/dizziness were more frequently recorded in older (≥7 year-old) children, whereas ataxia was more prevalent in younger (<7 year-old) children ($p<0.05$). No association was found between the frequency of any symptom and the metastatic stage.

3.2. Association of prediagnostic symptomatic interval with clinical and biological patient and disease characteristics

The median PSI of all patients was 2.0 months (range, 0.1 - 48.0 months; interquartile range, 1.0 - 3.0 months) (Table 3, Figure 1). The two clinical factors displaying the strongest statistical association with PSI were metastasis stage and age: Patients with lower-stage disease and patients with older age at diagnosis had longer PSIs than those with higher-stage disease ($p=0.075$, Figure 2) or younger age ($p=0.009$, Figure 3), respectively. No association was found between PSI and sex, completeness of resection, or histological subtype. Patients with a higher c-myc mRNA expression level had a trend towards a higher PSI ($p=0.085$), no association was found between PSI and TrkC mRNA level. Apart from vomiting, which was associated with a shorter PSI ($p=0.028$), no associations were found between PSI and other symptoms (Table 3).

3.3. Survival probabilities according to prediagnostic symptomatic interval and other clinical factors

Survival rates were slightly higher in the group with the longest PSI (Table 4, Figure 4). When the patient group with the longest PSI (4.0 – 48.0 months) was compared to those with a shorter PSI (0 – 3.9 months), 10-year PFS probabilities were 66 and 56%, respectively (p=0.202), and 10-year OS probabilities were 71% and 61%, respectively (p=0.056). When only patients with M0 were analyzed, a similar result was found. Survival probabilities according to other factors are summarized in Table 4.

In a multivariable Cox-regression analysis, forward and backward stepwise selection both identified lower age at primary surgery, higher metastatic stage at diagnosis, and 'sandwich' therapy arm as independent risk factors for lower PFS and OS probabilities. Higher expression of c-myc mRNA and lower expression of TrkC mRNA were retained in the backward selection only. In accordance to univariable analysis, longer duration of PSI was not shown to be associated with adverse outcome.

4. DISCUSSION

Due to its rarity and the non-specificity of symptoms and signs, childhood cancer frequently poses a major diagnostic challenge. This often results in PSIs in the range of several weeks to months.[5-9, 11, 15, 28-30] Both the symptoms and the uncertainty of their origin can contribute to significant stress and suffering in patients and their parents/carers.[12] Patients and physicians often speculate on whether an earlier diagnosis would have led to a less advanced disease stage and ultimately to a better prognosis, and alleged delay in diagnosis is a frequent source of medical malpractice lawsuits.[13-14] However, published data on the effect of the PSI on the outcome in children with brain tumors and specifically medulloblastomas are still limited and inconclusive.

To study the association of the PSI with disease stage at diagnosis, tumor control and survival outcome, we analyzed prospectively collected data on 224 well-documented patients with medulloblastoma aged 3 - 18 years at diagnosis treated within the multicenter trial HIT'91.[2] Median PSI of 2.0 months (range, 0.1 - 48.0 months) as well as nature and prevalence of the presenting symptoms and signs were comparable to those in other series.[4-8, 11, 15, 18, 20, 23] Contrary to common belief that a longer PSI is associated with more extensive disease, we found that patients with metastatic disease at presentation had a shorter median PSI than those without metastases (1.0 month vs. 2.0 months, $p = 0.094$). These results are in accordance with data by Halperin et al., who retrospectively analyzed 108 patients with medulloblastoma, in whom they found a median PSI of 8 weeks in patients with low-stage disease and of 4 weeks in those with high-stage disease.[6] A retrospective analysis of 166 patients with medulloblastoma by Brasme et al. found similar results

with a median PSI of 2 months (range, 0 - 15 months). To correlate PSI with tumor control and survival outcome, we compared survival probabilities of patients with longer PSIs (i.e. ≥4 months) with those of patients with shorter PSI. Interestingly we did not find an impaired prognosis in patients with the longest PSI, on the contrary, these patients had a tendency towards a superior outcome regarding overall survival (10-year OS 71% vs. 61%, p=0.056). Whereas the series published by Halperin et al. did not report any survival data, Kukal et al. found a significantly better progression-free and overall survival rate in the patient group with the longest PSI when combining all brain tumor histologies. No difference in survival according to PSI within any subgroup of uniform histology, including within the 57 patients with medulloblastoma, was found. However, this study had several limitations (small patient number, retrospective data collection, heterogeneity of patient, disease and treatment characteristics, and prolonged period of patient enrollment).

As in some studies the presence of post-operative residual tumor is an independent risk factor for tumor progression and death in patients with non-metastatic disease,[31] we hypothesized that a longer PSI may lead to a compromised resectability in this patient group. However, we could not detect any difference in PSI between those patients with any residual tumor and those without. Setting the cut-off to a residual tumor size of 1.5 cm^2 yielded similar results.

These results may seem counterintuitive, as one might expect longer PSIs to be associated with inferior survival, possibly caused by a more advanced disease stage by the time of diagnosis and/or a lower rate of gross-total tumor resection achieved. The association of a longer PSI with a lower metastatic stage and the trend towards a better progression-free and overall survival outcome are most probably explained by

the biology of the disease. Medulloblastoma comprises a group of biologically highly heterogeneous diseases displaying a broad variability of clinical behavior.[27, 32-35] Aggressive tumor growth may lead to more rapid clinical deterioration and hence to diagnosis within a shorter time period as compared to tumors with less aggressive growth characteristics. We could not find an association between PSI duration and histological subtype in our series, which however could be explained by the small patient number with non-classic histology. Apart from histology, other biologic markers are of known prognostic significance in medulloblastoma.[27, 36-38] When comparing the PSIs of those patients with high c-myc mRNA expression (a negative prognostic marker) to those with lower expression, we found a trend towards a shorter PSI in those patients with higher c-myc expression ($p=0.073$), supporting to a certain degree our hypothesis that a biologically more aggressive disease may translate into a shorter PSI. A corresponding trend could not be demonstrated for TrkC mRNA expression. As c-myc and N-myc DNA amplification[27] were only present in 5 patients each, we did not consider any corresponding analysis meaningful. These results however do not disprove the hypothesis that tumor biology may explain these counterintuitive results, as our analyses were limited by relatively small patient numbers with non-classic histology or available tissue for molecular analyses, and furthermore, histological subtype and c-myc/TrkC mRNA expression levels constitute only a small part of biological markers related to aggressiveness of disease.

In our series older children and adolescents had longer PSIs than younger ones. This is in accordance with other studies of children with brain tumors or other neoplasms.[6-8, 15, 20, 23] A possible explanation is the association of younger age with more aggressive tumor biology, but also increased awareness of parents for health changes in smaller children, higher frequency of routine medical consultations at

young age, or dissimulation of symptoms in adolescence may contribute to this finding. In accordance with other series,[6-7, 11] we could not detect an association of gender with PSI.

Our study has several strengths: To our knowledge this is the largest and the only prospective study addressing the question whether the PSI is associated with stage at diagnosis and outcome in pediatric patients with medulloblastoma or any other brain tumor disease of homogeneous histology. Our patient population, which constitutes a representative sample of same-aged patients with medulloblastoma diagnosed at that time[39] is well defined in terms of patient, disease, and treatment characteristics, with complete disease staging (including spinal MRI and CSF cytology) for most and central histopathological review available for all patients (an analysis of all 266 [95%] patients with available PSI value regardless of the availability of a central histopathological review yielded similar results). In addition, it is the first study evaluating the influence of biological markers on PSI in pediatric brain tumor patients. A limitation of our study is the lack of neurological, neuropsychological, and quality of life outcome information. One might for instance speculate that in a subgroup of patients with obstructive hydrocephalus a longer exposure to intracranial hypertension before diagnosis could lead to an adverse neuropsychological outcome.[40] As only recently medulloblastoma trials have started prospectively collecting neuropsychological and quality of life outcome data, such issues may be addressed in the future. A further limitation, which applies to all PSI studies, is the lack of an objective measure of the PSI duration. We believe that the judgment of the treating oncologist based on clinical history and examination(s), as used in our analysis, is the best estimate of the true PSI. We cannot exclude under- or overestimations of the PSI in individual patients. However, the possibility of recall

bias was minimized by the prospective nature of data collection, as the case report forms were completed at enrollment in the trial. Another limitation is the incomplete number of tumor samples available for expression analysis of c-myc and TrkC mRNA, and the lack of data on beta-catenin status, one of the best characterized biological prognostic factors in medulloblastoma.[38] Future trials incorporating tumor material collection for biological studies are warranted to further explore such correlations.

In conclusion, a longer PSI was associated with lower metastatic stage at presentation and a trend towards higher progression-free and overall survival probabilities. These findings may help to reassure parents or physicians, who are often concerned about the question whether an earlier diagnosis would have resulted in a better prognosis, and they may be of use in the context of medical malpractice accusations. Nevertheless they certainly do not contradict the importance of a timely diagnosis, as uncertainty and prolonged symptoms can be difficult to tolerate and as any negative effects of a diagnostic delay on neurological, neuropsychological, or quality of life outcome cannot be excluded. Furthermore, in an individual patient a diagnostic delay can result in dismal outcome, for instance through life-threatening complications of intracranial hypertension. This underscores the paramount importance of an early diagnosis of pediatric brain tumor disease.

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TABLES AND FIGURES

Table 1: Patient and disease characteristics

Number of patients	224
Age (median, range)	7.5 (2.9 – 17.5) years
Follow-up time of survivors (median, range)	11.8 (1.9 – 17.3) years
Gender	
Male	143 (64%)
Female	81 (36%)
Histological subtype	
Classic	204 (91%)
Desmoplastic	15 (7%)
Large cell/anaplastic	5 (2%)
c-myc mRNA expression	
≤1	46 (21%)
>1	51 (23%)
No value available	127 (57%)
TrkC mRNA expression	
≤1	77 (34%)
>1	20 (9%)
No value available	127 (57%)
c-myc/TrkC mRNA expression	
≤1/>1	7 (3%)
>1/≤1	38 (17%)
Others	52 (23%)
No value available	127 (57%)
Stage	
M0	111 (50%)
M1	33 (15%)
M2/3	40 (18%)
Incomplete staging	40 (18%)
Residual tumor	
- all patients	
No	163 (73%)
Yes	61 (27%)
- only patients with M0	
No	80 (72%)
Yes	31 (28%)
- thereof with size ≥1.5 cm^2	6 (5%)
Postoperative treatment	
'Sandwich'	125 (56%)
'Maintenance'	99 (44%)

Table 2: Presenting symptoms

Symptom	All patients (n=224)	Patients <7 years at diagnosis (n= 87)	Patients ≥7 years at diagnosis (n=137)	p-value[a]
	Number (percentage)	Number (percentage)	Number (percentage)	
Headache	125 (56%)	37 (43%)	88 (64%)	0.002
Vomiting (±nausea)	125 (56%)	54 (62%)	71 (52%)	0.167
Ataxia	48 (21%)	27 (31%)	21 (15%)	0.007
Diplopia/squint	15 (7%)	5 (6%)	10 (7%)	0.787
Vertigo/dizziness	13 (6%)	1 (1%)	12 (9%)	0.018
Head tilt	6 (3%)	1 (1%)	5 (4%)	-
Fatigue	5 (2%)	2 (2%)	3 (2%)	-
Somnolence/loss of consciousness	4 (2%)	0 (0%)	4 (3%)	-
Nausea (without vomiting)	3 (1%)	0 (0%)	3 (2%)	-
Visual symptoms (NOS or other than diplopia/squint)	3 (1%)	1 (1%)	2 (2%)	-
Cervical pain	2 (1%)	2 (2%)	0 (0%)	-
Concentration impairment	2 (1%)	0 (0%)	2 (2%)	-
Facial nerve paralysis	2 (1%)	1 (1%)	1 (1%)	-
Abdominal pain	1 (<1%)	1 (1%)	0 (0%)	-
Abnormal weight gain	1 (<1%)	1 (1%)	0 (0%)	-
Back pain	1 (<1%)	1 (1%)	0 (0%)	-
Constipation	1 (<1%)	1 (1%)	0 (0%)	-
Leg weakness	1 (<1%)	1 (1%)	0 (0%)	-
Night sweats	1 (<1%)	0 (0%)	1 (1%)	-
Rapid growth of head	1 (<1%)	1 (1%)	0 (0%)	-
Seizure	1 (<1%)	1 (1%)	0 (0%)	-
Slurred speech	1 (<1%)	0 (0%)	1 (1%)	-
Tinnitus	1 (<1%)	0 (0%)	1 (1%)	-
[a]Fisher's exact test (only for symptoms with a prevalence of ≥5%) NOS, not otherwise specified				

Table 3: Prediagnostic symptomatic interval in relation to age, gender, histology, c-myc and TrkC mRNA expression, stage, postoperative residual tumor status, and presenting symptoms

	PSI [months] median (range)	p-value (log-rank test)
All patients (n=224)	2.0 (0.1 – 48.0)	
Age at diagnosis		0.009
3 to 8 years (n=127)	1.0 (0.1 – 48.0)	
8 to 13 years (n=64)	2.0 (0.1 – 48.0)	
13 to 18 years (n=33)	3.0 (0.5 – 48.0)	
Gender		0.223
Male (n=143)	1.0 (0.1 – 48.0)	
Female (n=81)	2.0 (0.1 – 48.0)	
Histological subtype		0.220
Classic (n=204)	2.0 (0.1 – 48.0)	
Desmoplastic (n=15)	1.0 (0.5 – 7.0)	
Large cell/anaplastic (n=5)	1.0 (0.3 – 3.0)	
c-myc mRNA expression		0.073
≤1 (n=46)	2.0 (0.1 – 24.0)	with available value only:
>1 (n=51)	1.0 (0.1 – 6.0)	0.085
No tissue available for analysis (n=127)	2.0 (0.3 – 48.0)	
TrkC mRNA expression		0.283
≤1 (n=77)	2.0 (0.1 – 15.0)	with available value only:
>1 (n=20)	1.0 (0.1 – 24.0)	0.747
No tissue available for analysis (n=127)	2.0 (0.3 – 48.0)	
Stage		0.145
M0 (n=111)	2.0 (0.1 – 48.0)	complete staging only:
M1 (n=33)	2.0 (0.3 – 9.0)	0.075
M2/3 (n=40)	1.0 (0.3 – 6.0)	M0/1 vs. M2/3:
Incomplete staging (n=40)	1.0 (0.1 – 48.0)	0.025
Residual tumor		
- all patients, residual any size		0.595
No (n=163)	1.5 (0.1 – 48.0)	
Yes (n=61)	2.0 (0.3 – 15.0)	
- only M0, residual any size		0.495
No (n=80)	1.0 (0.1 – 48.0)	
Yes (n=31)	2.0 (0.5 – 15.0)	
- only M0, residual ≥1.5 cm^2		0.605
No (n=105)	2.0 (0.1 - 48.0)	
Yes (n=6)	3.0 (2.0 – 5.0)	
Presenting symptom[a]		
Headache		0.685
present (n=125)	1.0 (0.1 – 48.0)	
absent (n=99)	2.0 (0.1 – 15.0)	
Vomiting		0.028
present (n=125)	1.0 (0.3 – 48.0)	
absent (n=99)	2.0 (0.1 – 48.0)	
Ataxia		0.100

present (n=48)	1.0 (0.1 – 15.0)	
absent (n=176)	2.0 (0.1 – 48.0)	
Diplopia/squint		0.916
present (n=15)	2.0 (0.3 – 9.0)	
absent (n=209)	2.0 (0.1 – 48.0)	
Vertigo/dizziness		0.501
present (n=13)	3.0 (0.3 – 8.0)	
absent (n=211)	2.0 (0.1 – 48.0)	
[a]Only symptoms with a prevalence of ≥5%. PSI, prediagnostic symptomatic interval		

Table 4: Survival probabilities according to prediagnostic symptomatic interval and other clinical and biological factors

	10-year PFS (SE) [%]	p-value (log-rank test)	10-year OS (SE) [%]	p-value (log-rank test)
All patients (n=224)				
	58 (3)		63 (3)	
PSI		0.505		0.244
0 – 0.9 months (n=40)	63 (8)		64 (8)	
1.0 – 1.9 months (n=70)	55 (6)		63 (6)	
2.0 – 3.9 months (n=66)	54 (6)		57 (6)	
4.0 – 48.0 months (n=48)	66 (7)		71 (7)	
PSI, only patients with M0		0.741		0.304
0 – 0.9 months (n=19)	68 (11)		72 (11)	
1.0 – 1.9 months (n=32)	68 (8)		75 (8)	
2.0 – 3.9 months (n=34)	61 (9)		64 (8)	
4.0 – 48.0 months (n=26)	73 (9)		80 (8)	
Age at diagnosis		0.070		0.036
3 to 8 years (n=127)	53 (5)		60 (4)	
8 to 13 years (n=64)	58 (6)		61 (6)	
13 to 18 years (n=33)	79 (7)		81 (7)	
Gender		0.680		0.532
Male (n=143)	58 (4)		64 (4)	
Female (n=81)	59 (6)		61 (6)	
Histological subtype		0.953		0.934
Classic (n=204)	58 (4)		62 (4)	
Desmoplastic (n=15)	67 (12)		66 (12)	
Large cell/anaplastic (n=5)	60 (22)		80 (18)	
c-myc mRNA expression		0.120		0.438
≤1 (n=46)	70 (7)	with available	72 (7)	with available
>1 (n=51)	53 (7)	value only:	59 (7)	value only:
No value available (n=127)	57 (5)	0.041	62 (4)	0.191
TrkC mRNA expression		0.376		0.218
≤1 (n=77)	57 (6)	with value only:	61 (6)	with value only:
>1 (n=20)	75 (10)	0.172	80 (9)	0.079
No value available (n=127)	57 (5)		62 (4)	
Stage		0.021		0.007
M0 (n=111)	67 (5)		72 (4)	
M1 (n=33)	54 (9)		54 (9)	
M2/3 (n=40)	42 (8)		45 (8)	
Incomplete staging (n=40)	54 (8)		64 (8)	
Residual tumor				
- all patients, residual any size		0.135		0.241
No (n=163)	60 (4)		65 (4)	
Yes (n=61)	54 (6)		59 (6)	
- only M0, residual any size		0.667		0.987
No (n=80)	67 (5)		71 (5)	
Yes (n=31)	68 (8)		74 (8)	
- only M0, residual ≥1.5 cm^2		0.822		0.932

No (n=105)	66 (5)		71 (5)	
Yes (n=6)	83 (15)		83 (15)	
Postoperative treatment		0.034		0.016
'Sandwich' (n=125)	51 (5)		57 (5)	
'Maintenance' (n=99)	67 (5)		71 (5)	
OS, overall survival rate; PFS, progression-free survival rate; PSI, prediagnostic symptomatic interval; SE, standard error				

FIGURE LEGENDS

Figure 1: Cumulative distribution of the prediagnostic symptomatic interval for all 224 patients with medulloblastoma

Figure 2: Cumulative distributions of the prediagnostic symptomatic intervals in all 224 patients with medulloblastoma according to disease stage (M0, no metastases; M1, only microscopic cerebrospinal fluid metastases; M2/M3, macroscopic cerebral and/or spinal metastases) for those 184 patients with complete staging (M0 vs. M1 vs. M2/M3, p=0.075; M0 vs. M1/M2/M3, p=0.025; log-rank test)

Figure 3: Cumulative distributions of the prediagnostic symptomatic intervals according to the age groups at diagnosis for all 224 patients with medulloblastoma (p=0.009, log-rank test)

Figure 4: Overall survival (OS) probabilities for all 224 patients with medulloblastoma according to the prediagnostic symptomatic interval (PSI): 10-year OS for PSI of 0 to 0.9 months (group1), 64%; 1.0 to 1.9 months (group 2), 63%; 2.0 to 3.9 months (group 3), 57%; 4.0 to 48.0 months (group 4), 71% (p=0.244, log-rank test).

Figure 1

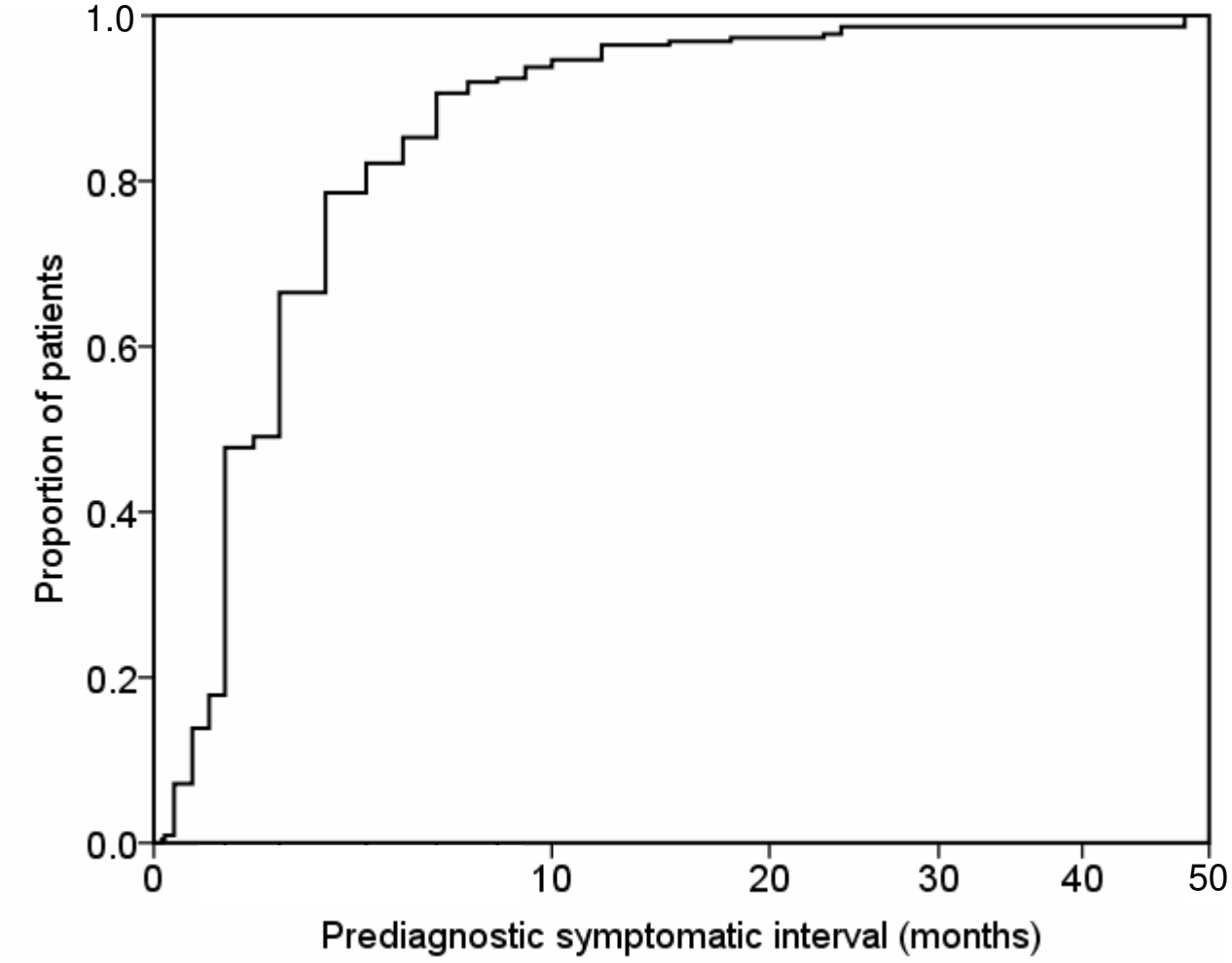

1.0
0.8
0.6
0.4
0.2
0.0
Proportion of patients
0
10
20
30
40
50
Prediagnostic symptomatic interval (months)

Figure 2

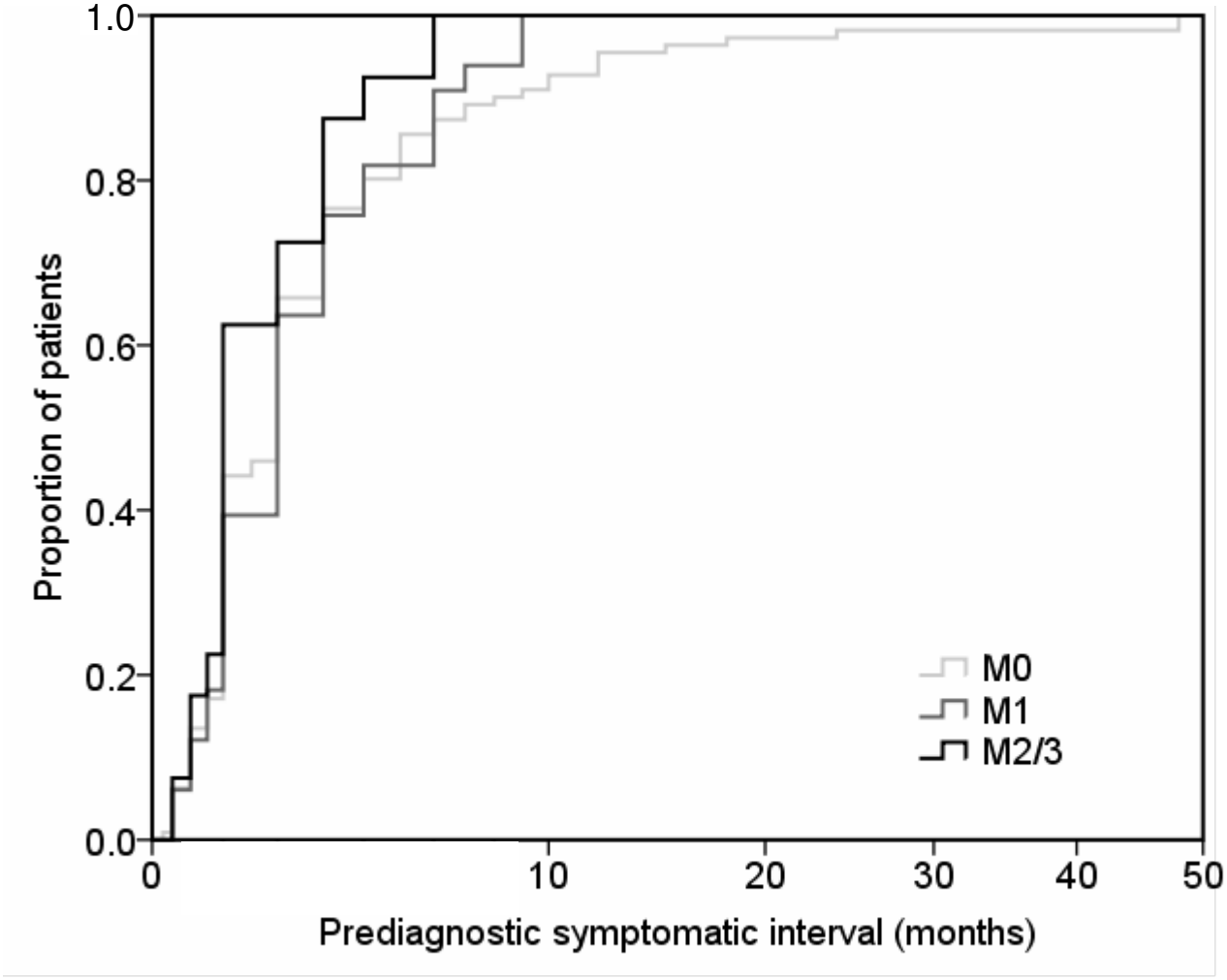

1.0
0.8
0.6
0.4
0.2
0.0
Proportion of patients
0
10
20
30
40
50
Prediagnostic symptomatic interval (months)
M0
M1
M2/3

Figure 3

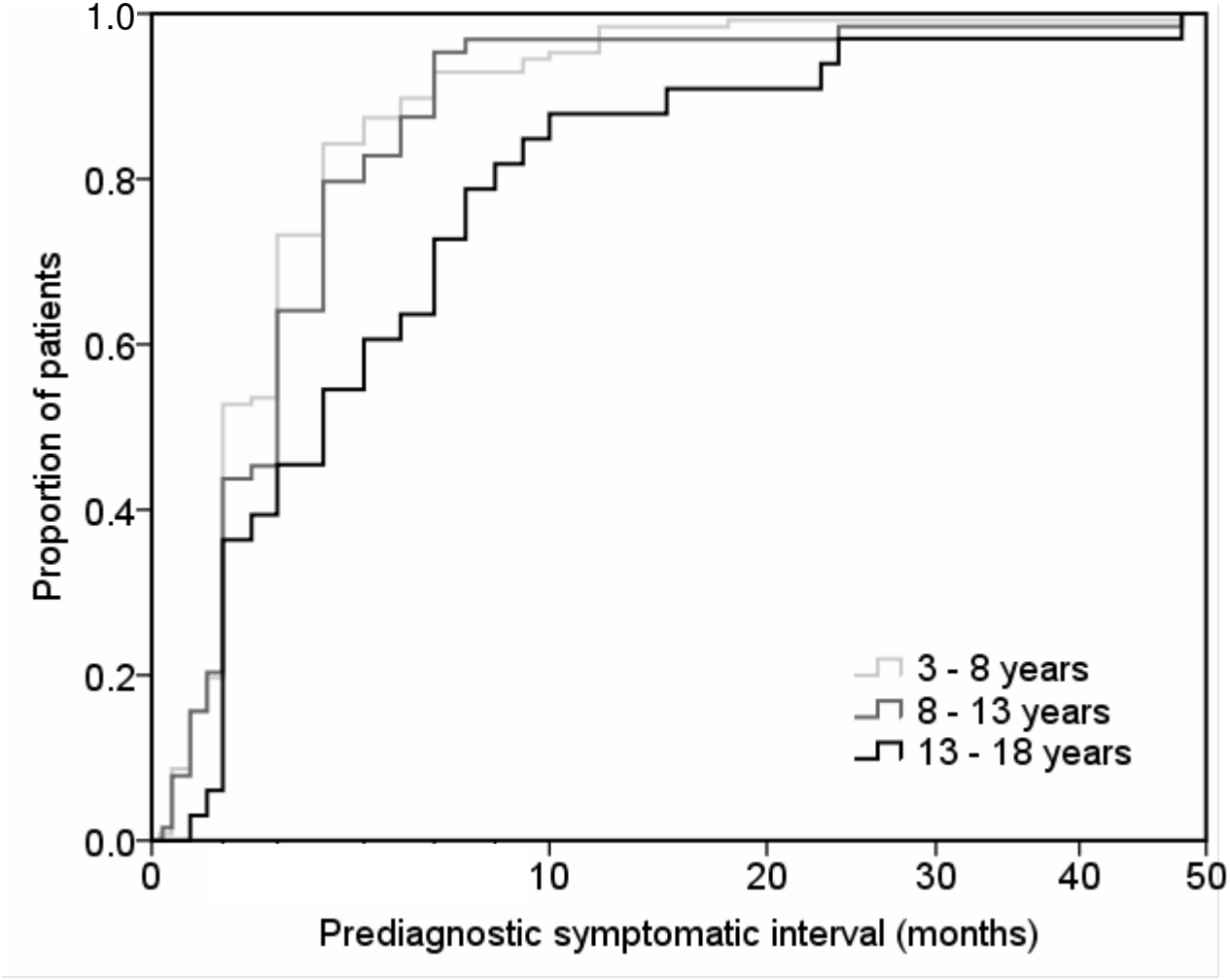
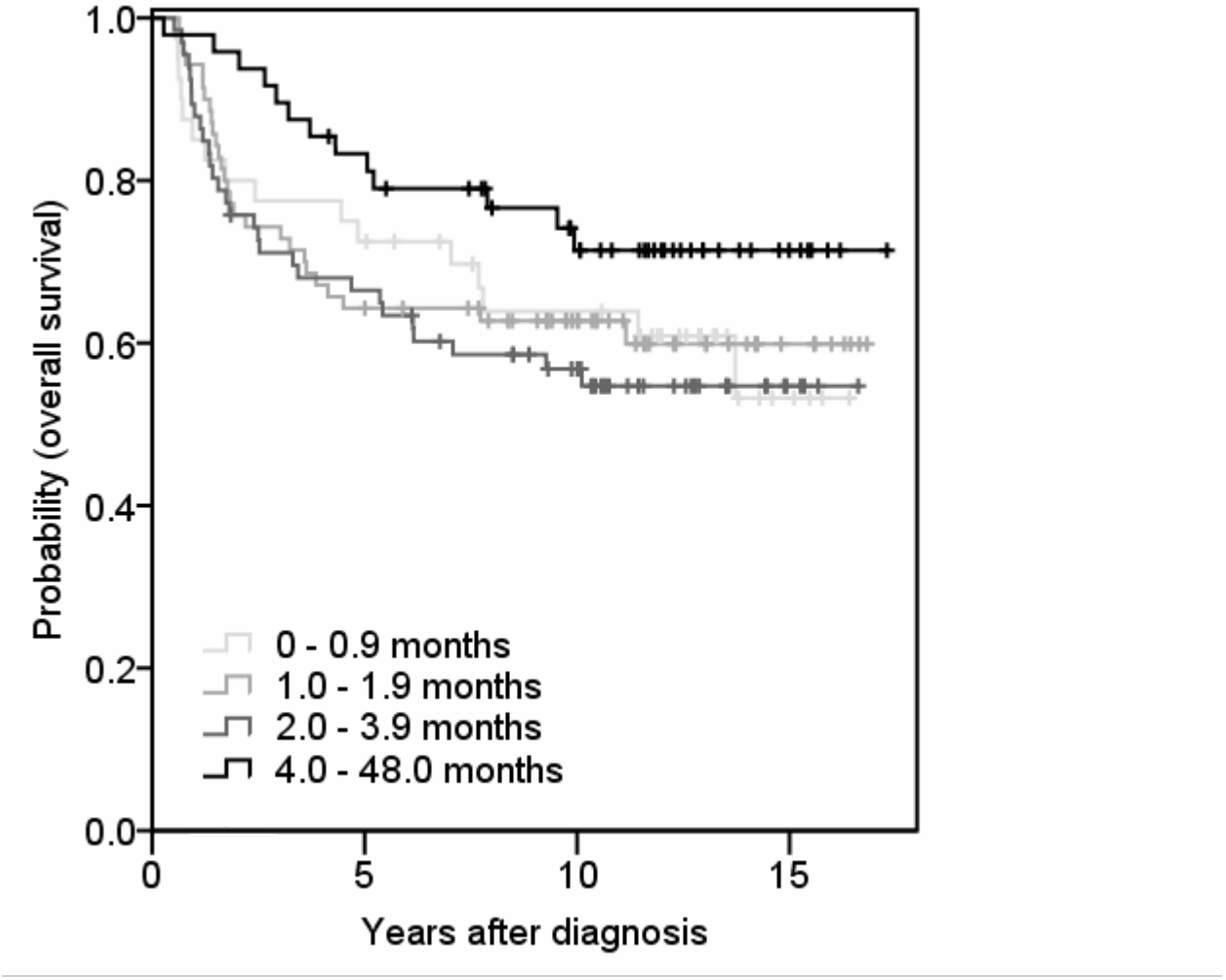

1.0
0.8
0.6
0.4
0.2
0.0
Proportion of patients
0
10
20
30
40
50
Prediagnostic symptomatic interval (months)
3 - 8 years
8 - 13 years
13 - 18 years

Figure 4


1.0
0.8
0.6
0.4
0.2
0.0
Probability (overall survival)
0 - 0.9 months
1.0 - 1.9 months
2.0 - 3.9 months
4.0 - 48.0 months
0
5
10
15
Years after diagnosis